Renal Failure: I. The Effect of Complete Renal Artery Occlusion for Variable Periods of Time as Compared to Exposure to Sub-filtration Arterial Pressures Below 30 mm Hg for Similar Periods * †

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MANY medical investigators and clinicians have observed that acute renal failure (lower nephron nephrosis) frequently follows hemorrhage, burns, dehydration, trauma, incompatible blood transfusions and peripheral circulatory failure. Mallory, after studying 260 cases of battle injury, has shown that injury to the ascending limb of the loop of Henle occurs within 24 hours and that after four to five days, necrosis and regeneration of tubular epithelium has begun in the ascending limbs and distal tubules. However, the exact precipitating factor or factors which produce acute renal failure remain unknown. It has been suggested that during shock, a nephrotoxic substance is released which subsequently causes renal failure. Other investigators have suggested that renal failure is a result of mechanical blocking of the kidney tubules with hemoglobin or a heme derivative.[5] Darmady,[1] Maegraieth and Findley[6] and many other investigators have suggested that renal failure is due to ischemia as a result of shock. Van Slyke[11] and others[4, 10] have shown that renal ischemia, as produced by occlusion of the renal artery in animals, is followed by renal failure; either transitory or fatal, depending on the duration of the ischemia.

In a previous study[8] the authors noted that occlusion of the aorta proximal to the renal arteries resulted in a mean blood pressure below 30 mm Hg in the distal segment. Although renal clearances were zero during the periods of occlusion, this pressure seemed to be adequate to prevent immediate renal damage as demonstrated by renal clearance studies which returned toward normal values a few hours after removal of the aortic occlusion. In the light of these observations and the fact that irreversible shock develops at an arterial blood pressure of 30 to 35 mm. Hg or above (usually of shorter duration than that of the current experiments), it seemed worthwhile to study in detail the renal functional response to arterial blood pressure below the threshold of filtration as compared to complete renal arterial occlusion. In addition, rather than study the immediate effect, it was thought best to determine renal function at a time when maximal renal damage would be expected to occur as shown by Mallory.[7] Thus, this experiment was designed to determine what effects, if any, reduced pressures, for prolonged periods

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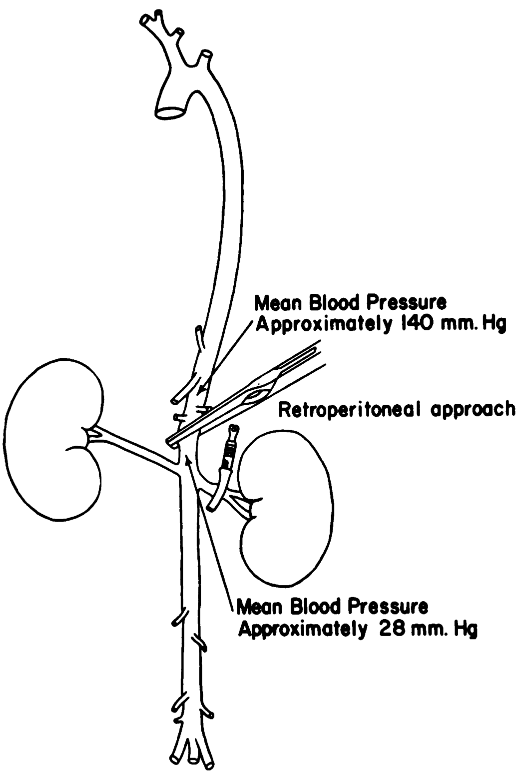

FIG. 1. Diagrammatic representation of the method for producing renal occlusion by the three different methods. Group I. Aortic occlusion above the renal arteries. Group II. Renal arterial occlusion alone. Group III. Aortic plus renal arterial occlusion simultaneously.

of time, equivalent to those found in irreversible shock might have on the kidney, and to compare these effects with those on a kidney made ischemic by complete occlusion of the renal artery (as was done by previous investigators) for the same period of time.

METHODS

Seventy-nine female dogs varying in weight from 8.0 Kg. to 20.0 Kg. were used in the experiment. They were divided into three large groups, and each of these were divided into sub-groups depending on the various vascular occlusion periods. Group 1 contained 18 dogs in which the aorta was occluded proximal to the origin of the renal arteries (Fig. 1); Group 2 contained 37 dogs in which one renal artery was occluded; and Group 3 contained 24 dogs in which the aorta was occluded as in Group 1 but in which, in addition, one renal artery was occluded simultaneously (Fig. 1).

All dogs were anesthetized with pentobarbital sodium (30 mg./Kg.). Approximately one hour before the renal studies were begun, each dog was hydrated with water (40 ml./Kg.) via gastric tube or infused for one hour with 5 per cent glucose (20 to 30 ml./Kg.). Renal hemodynamics and excretion of water and electrolytes were then determined on each dog. Creatinine was used to determine glomerular filtration rate (GFR). Para-aminohippurate (PAH) was used to determine renal plasma flow (RPF). Mean arterial blood pressure was determined by direct intra-arterial mercury manometry. Three consecutive 10 minute periods were taken on each dog and these served as control observation on renal function. Urine volume was measured and the sodium and potassium content in the plasma and urine were determined using a Model D-U Beckman flame photometer. Arterial blood collected through a manifold was used for analysis. The general methods and analytical procedures have been described previously.[3, 9] Immediately following the three 10 minute control periods, each dog was operated on using aseptic technic.

Group 1: There were 18 dogs in Group 1 in which only the aorta was occluded proximal to the renal arteries. An oblique incision was made at the costo-vertebral angle just distal to the lowest rib on the left side. By remaining retro-peritoneal, the aorta was exposed and, using a Pott's clamp, was occluded proximal to the origin of both renal arteries for varying intervals. In five dogs (Sub-group 1A) the aorta was occluded for one hour; in seven dogs(Sub-group 1B) it was occluded for one hour and 30 minutes and in six dogs (Sub-group 1C) it was occluded for two hours. During the period of occlusion, the average mean blood pressure in the distal segment was obtained by direct intra-arterial mercury manometry. An occlusion period of three hours was not employed on the animals in which the aorta alone was occluded since the animals in Group 3 (Sub-group 3C) served for this purpose. In these animals (Group 3), the right kidney was exposed to aortic occlusion only for three hours. Occlusion periods up to two hours on the animals in Group 3 (using the observations on the kidney exposed to aortic occlusion only) confirmed the observations on the animals in Group 1 and, therefore, we considered it unnecessary duplication to do more experiments on aortic occlusion alone (Group 1) for periods in excess of two hours.

Group 2: There were 37 dogs in Group 2 of which 10 were subjected to unilateral occlusion of the renal artery for 60 minutes (Sub-group 2A), seven for 90 minutes (Sub-group 2B), 13 for two hours (Sub-group 2C) and seven for three hours (Sub-group 2D). In these animals an oblique incision was made at the costo-vertebral angle just distal to the left rib alternately on the right and then on the left side, depending on which renal artery was to be occluded. Through a retro-peritoneal approach the renal artery was exposed and then occluded for the intervals described above, using a Bulldog vascular clamp.

Group 3: There were 24 dogs in Group 3 in which the aorta and one renal artery were occluded simultaneously. The same operative technic was used as in Group 1. The aorta was exposed as was the left renal artery. Both were occluded simultaneously and remained occluded for the same period of time. The occlusion period was two hours in eight dogs (Sub-group 3A), two hours and 30 minutes in six dogs (Sub-group 3B), and three hours in 10 dogs (Sub-group 3C). The aortic clamp was placed above the origin of both renal arteries so as to be certain that circulation to the right kidney was not interrupted. The average mean blood pressure in the distal segment was measured as noted above for the dogs in Group 1.

Following the period of occlusion in each dog the clamps were removed. The reestablishment of circulation through the occluded renal artery was ascertained by observing pulsations in the artery distal to the occlusion. Then the incision was closed and procaine penicillin G (300,000–600,000 units) was injected intramuscularly.

After an interval of three to five days, follow up renal studies were done on each dog. Renal hemodynamics and excretion of water and electrolytes were determined as described above. In Group 1 the follow up study consisted of three 10 minute periods as was done during the control study and a comparison made between control renal function and that following aortic occlusion. In Groups 2 and 3, each ureter was catheterized with polyethylene tubing and renal function determined for each kidney separately. Three consecutive 10 minute periods were collected as during the control observations. Control values for each kidney in the dogs in Groups 2 and 3 were derived by assuming that each kidney in the normal animal contributes approximately one-half to the total renal function.* Having made this assumption, we used one-half of the values (1/2C—Tables 2A to 3B) for both kidneys as representing the control function for each kidney. A comparison was then made between the control values for each kidney and the observations made three to five days after the occlusion. In Groups 2 and 3, the occluded and the unoccluded kidney were also sta-

* There is no question about the validity for the animals in Group 2 since the arteries to alternate kidneys were occluded in successive experiments. In the animals in Group 3 there may be minor objections to this assumption since, for technical reasons, the left kidney was always the one which was occluded. However, the magnitude of the change in this group of experiments was such that minor differences in control values between the kidneys would have been of little if any significance.

TABLE 1A. *Effect of Aortic Occlusion Only on Renal Hemodynamics (3 to 4 Days After Occlusion)*

Dog Number	Mean Blood Pressure mm. Hg C	Mean Blood Pressure mm. Hg D_1	Glomerular Filtration Rate ml./min. C	Glomerular Filtration Rate ml./min. D_1	Renal Plasma Flow ml./min. C	Renal Plasma Flow ml./min. D_1	Renal Blood Flow ml./min. C	Renal Blood Flow ml./min. D_1	Hematocrit C	Hematocrit D_1	Duration of Occlusion (Minutes)	Days from Clamp to D_1	Femoral MBP‡ During Clamp	Body Wt. in Kilograms
Subgroup 1A—Occlusion Time = 1 hour														
23–A.O.	141	146	72	79	208	259	378	424	45	39	60	4	30	18.5
24–A.O.	137	125	60	61	184	186	368	286	50	35	60	4	19	16.0
25–A.O.	123	80	49	73	200	288	328	457	39	37	60	3	30	18.5
26–A.O.	139	141	50	77	199	291	375	428	47	32	60	4	22	18.5
27–A.O.	116	140	39	34	143	92	234	128	39	28	60	4	24	11.0
Mean	131	126	54	65	187	223	337	345	44	34	60	4	25	
% of Control		96		120		119		102		77				
P Value* <		.50		.10		.30		.50		.05				
Subgroup 1B—Occlusion Time = 1½ hours														
28–A.O.	136	134	43	61	182	174	260	245	30	29	90	3	29	17.5
29–A.O.	134	127	57	35	193	101	293	153	34	34	90	3	17	18.5
30–A.O.	138	135	58	45	218	236	346	352	37	33	90	3	28	18.0
31–A.O.	135	117	64	54	258	151	437	213	41	29	90	3	22	18.0
32–A.O.	139	81	45	44	158	175	251	246	37	29	90	3	18	15.0
33–A.O.	135	135	67	67	166	175	286	265	42	34	90	3	20	20.0
34–A.O.	101	119	45	52	142	140	190	188	25	25	90	3	26	17.0
Mean	131	121	54	51	188	165	295	237	35	30	90	3	23	
% of Control		92		94		88		80		86				
P Value* <		.40		.50		.10		.10		.05				
Subgroup 1C—Occlusion Time = 2 hours														
35–A.O.	124	96	68	69	232	217	363	350	36	38	120	3	31	18.0
36–A.O.	124	131	58	61	180	161	257	264	30	39	120	3	28	16.0
37–A.O.	132	115	49	45	163	152	267	267	39	43	120	3	22	13.0
38–A.O.	116	95	75	64	245	235	408	346	40	32	120	3	21	18.0
39–A.O.	126	118	58	29	173	94	237	136	27	31	120	3	—	16.0
40–A.O.	140	137	41	45	127	154	235	233	46	34	120	3	20	10.0
Mean	127	115	58	52	187	169	295	266	36	36	120	3	24	
% of Control		91		90		90		90		100				
P Value* <		.10		.30		.30		.20		.50				

‡ = Mean Blood Pressure in mm. Hg.
C = Control Observations—average of 3–10 minute periods.
D_1 = Observations made 3 to 4 days after occlusion—average of 3–10 minute periods.
* $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$; statistical analysis by R. A. Seibert.

tistically compared with each other. The unoccluded kidney in Group 2 served as an absolute control on the method and the operative technic since nothing was done to interrupt the blood supply to this kidney. In Group 3 the effect of aortic occlusion only (right kidney) can be compared to the control values and to the effect of simultaneous aortic occlusion and renal artery occlusion in the opposite kidney. At the end of each experiment the animals were sacrificed and pathologic studies were made on both kidneys.

RESULTS

The results of aortic occlusion only (Group 1) are shown in Tables 1A and 1B. Occlusion of the aorta for 60, 90 and 120 minutes had no significant effect on arterial blood pressure or on renal hemodynamics when the observations made three to five days after occlusion (D1) were compared with the control values (C). Likewise, there were no significant changes in glomerular filtration rate in any of the sub-groups in Group 1 and the findings were fairly consistent in all animals studied in this group with the exception of dogs Nos. 29 and 39 which showed a moderate drop in renal function following aortic occlusion.

As with the renal hemodynamics, aortic occlusion did not appear to alter excretion of water and electrolytes (Table 1B). Often times excretion of sodium was moderately reduced but this was not consistent enough to be statistically significant.

There was a decrease in concentration of plasma sodium ($p < 0.05$) when the post occlusion values are compared to the control values in Sub-groups 1A and 1B. The significance of this is not evident unless it represents a decreased intake of sodium due to loss of appetite and failure to eat during the postoperative period between the control observations and the follow up studies three to four days later. There was a slight increase in the plasma sodium concentration in the dogs in Sub-group 1C.

The mean values for the average mean blood pressure that existed in the distal segment of the aorta during the period of occlusion were 25 mm Hg (Sub-group 1A), 23 mm. Hg (Sub-group 1B), and 24 mm. Hg (Sub-group 1C), respectively, which represents 60, 90 and 120 minutes of aortic occlusion.

Referring to Tables 3A and 3B on which are recorded the data from the dogs in which the right kidney only was subjected to aortic occlusion for periods of two to three hours, further evidence is presented that aortic occlusion alone for periods up to three hours will not produce renal damage. Apparently, mean blood pressures of 16 to 30 mm. Hg at the level of the renal artery are adequate to protect the kidney against ischemic damage for periods up to three hours. This is in marked contrast to the observations made when the renal artery was completely occluded, either alone (Group 2) or simultaneously with the aorta (Group 3).

The results of unilateral occlusion of a renal artery only (Group 2) are shown in Tables 2A and 2B. The data show that no significant change occurred in the mean blood pressure from the control to the post occlusion observations as a result of occlusion of a renal artery for periods up to three hours. Each of the sub-groups of animals showed some evidence of renal damage on the side on which the renal artery was occluded as indicated by a significant reduction in glomerular filtration rate and renal blood flow in the occluded kidney. After only one hour of occlusion, glomerular filtration was depressed to 70% of control ($p < 0.01$) and renal blood flow to 69% of the control ($p < 0.01$). After two hours of occlusion, glomerular filtration rate for the sub-group was depressed to 55% of the control value ($p < 0.001$) and renal blood flow to 50% ($p < 0.001$) of the control. After three hours (Sub-group 2D) of occlusion, renal function was virtually non-existent in the occluded kidney of any of the

TABLE 1B. *The Effect of Aortic Occlusion Only on Excretion of Water and Electrolytes (3 to 4 Days After Occlusion)*

	URINE		PLASMA				URINE			
	Volume ml./min.		Sodium mEq/L		Potassium mEq/L		Sodium Excretion µEq/min.		Potassium Excretion µEq/min.	
Dog Number	C	D_1	C	D_1	C	D_1	C	D_1	C	D_1
Subgroup 1C—Occlusion Time = 1 hour										
23–A.O.	0.6	2.4	144	134	3.00	3.87	53	178	23	50
24–A.O.	1.0	1.8	149	131	3.02	3.97	72	119	27	53
25–A.O.	1.2	0.8	140	130	2.10	2.53	190	37	42	68
26–A.O.	1.5	0.8	161	144	3.84	3.76	82	112	37	31
27–A.O.	0.9	0.4	146	141	3.00	3.28	56	17	18	19
Mean	1.0	1.2	148	136	2.99	3.48	91	93	29	44
% of Control		120		92		116		102		152
P Value‡ <		.50		.01		.05		.50		.20
Subgroup 1B—Occlusion Time = 1½ hours										
28–A.O.	1.2	1.5	149	137	3.25	3.87	89	137	30	54
29–A.O.	1.2	1.5	144	141	3.61	3.51	49	37	34	35
30–A.O.	3.6	0.4	153	148	2.69	2.71	269	42	30	38
31–A.O.	1.8	0.2	155	137	2.87	3.17	285	12	43	28
32–A.O.	3.0	0.9	—	—	—	—	257	141	43	32
33–A.O.	1.1	0.7	138	134	2.71	2.87	90	41	32	48
34–A.O.	2.6	1.4	154	135	3.00	2.69	63	46	56	42
Mean	2.1	0.9	149	139	3.02	3.14	157	65	38	40
% of Control		43		93		104		41		105
P Value‡ <		.10		.05		.50		.10		.50
Subgroup 1C—Occlusion Time = 2 hours										
35–A.O.	2.2	1.6	151	156	3.38	3.30	206	144	41	53
36–A.O.	2.6	1.4	139	155	3.10	3.51	256	121	41	45
37–A.O.	1.4	0.8	141	152	2.84	3.74	53	68	22	20
38–A.O.	1.2	2.1	126	157	3.53	3.43	136	305	100	93
39–A.O.	3.3	1.9	139	152	3.28	3.35	306	80	40	29
40–A.O.	0.8	0.4	137	153	3.30	3.25	46	27	26	23
Mean	1.9	1.4	139	154	3.24	3.43	167	124	45	44
% of Control		74		111		106		74		98
P Value‡ <		.50		.05		.20		.50		.50

C, D_1—see Table 1A for key to abbreviations.

‡ $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$.

dogs, the glomerular filtration rate being reduced to 8% of the control ($p < 0.001$) for the group, and the renal blood flow to 12% of the control ($p < 0.001$). The difference in function between the occluded and unoccluded side was always statistically significant both for glomerular filtration rate as well as renal blood flow.

Interestingly enough, there was frequently an increase in glomerular filtration rate and renal blood flow in the unoccluded kidney over control levels. This response was statistically significant ($p < 0.05$) for periods of occlusion of 60 and 90 minutes and was most marked when the follow up studies were done four to five days after

TABLE 2A. *Effect of Renal Arterial Occlusion Only on Renal Hemodynamics*

Dog Number	Mean Blood Pressure mm. Hg C	Mean Blood Pressure mm. Hg D_1	Glomerular Filtration Rate ml./min. C	½C	D_1 CL	D_1 UC	Renal Plasma Flow ml./min. C	½C	D_1 CL	D_1 UC	Renal Blood Flow ml./min. C	½C	D_1 CL	D_1 UC	Hematocrit C	Hematocrit D_1	Wt. in Kilo-grams
Subgroup 2A—Occlusion Time = 1 hour																	
1 RA	117	128	49	25	16	43	209	105	60	162	373	187	88	238	44	32	15.4
2 RA	144	133	46	23	5	41	176	88	24	168	271	136	35	247	35	32	15.0
3 RA	126	131	68	34	13	52	170	85	47	170	340	170	84	304	50	44	16.4
4 RA	132	136	62	31	21	58	207	104	75	166	376	188	115	255	45	35	16.0
5 RA	140	134	56	28	33	36	179	90	111	111	309	155	173	173	42	36	17.0
6 RA	146	122	79	39	30	35	259	129	95	110	425	212	146	169	39	35	18.5
7 RA	125	130	61	31	25	36	186	93	92	127	286	143	153	212	35	40	16.0
8 RA	80	126	73	37	21	32	288	144	91	144	457	229	147	232	37	38	18.5
9 RA	141	135	77	38	31	39	291	146	129	155	428	214	161	194	32	20	18.5
10 RA	140	111	34	17	16	22	92	46	46	65	128	64	71	100	28	35	11.0
Mean	129	129	61	30	21	39	206	103	77	138	339	170	117	212	39	35	
% of Control		100			70	130			75	134			69	125		90	
P Value‡ <		.50			.01	.05			.05	.05			.01	.05		.10	
P Value# <						.001				.001				.001			
Subgroup 2B—Occlusion Time = 1½ hours																	
11 RA	134	145	61	30	1	30	174	87	4	95	245	123	5	125	29	24	17.5
12 RA	127	124	35	18	23	35	101	51	73	101	153	77	114	158	34	36	18.5
13 RA	135	158	45	23	23	27	136	68	72	81	203	102	104	117	33	31	18.0
14 RA	117	124	54	27	29	36	151	75	92	103	213	107	126	141	29	27	18.0
15 RA	81	122	44	22	13	28	115	58	35	75	162	81	49	104	29	28	15.0
16 RA	135	134	67	34	26	35	175	88	66	88	265	132	110	147	34	40	20.0
17 RA	119	90	52	26	25	30	140	70	67	80	187	94	96	114	25	30	17.0
Mean	121	128	51	26	20	32	142	71	58	89	204	102	86	129	30	31	
½ of Control		106			77	123			82	125			84	126		103	
P Value‡ <		.50			.30	.05			.40	.05			.50	.05		.50	
P Value# <						.05				.05				.05			
Subgroup 2C—Occlusion Time = 2 hours																	
18 RA	101	75	23	12	2	22	98	49	7	86	134	67	9	112	27	23	8.5
19 RA	122	101	37	19	0	25	106	53	0	86	166	83	0	126	36	32	15.6
20 RA	96	119	69	34	26	31	217	109	77	90	350	175	128	150	38	40	18.0
21 RA	131	140	61	30	20	30	161	81	46	69	264	132	74	111	39	38	16.0
22 RA	115	122	45	23	12	27	152	76	45	93	267	134	67	139	43	33	13.0

TABLE 2A—*Continued*

Dog Number	Mean Blood Pressure mm. Hg		Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit		Wt. in Kilo-grams
					D_1				D_1				D_1				
	C	D_1	C	½C	CL	UC	C	½C	CL	UC	C	½C	CL	UC	C	D_1	
							Subgroup 2C—*Continued*										
23 RA	95	96	64	32	30	32	235	117	90	93	346	173	129	133	32	30	18.0
24 RA	137	148	45	23	7	38	154	77	25	111	233	117	37	166	34	33	10.0
25 RA	93	73	41	21	6	21	125	63	33	62	187	94	47	89	33	30	10.0
26 RA	147	141	45	23	6	16	127	64	19	60	276	139	40	125	54	52	12.0
27 RA	127	101	34	17	8	9	80	40	29	35	163	82	51	61	51	43	13.0
28 RA	120	124	25	13	23	24	103	52	70	77	240	121	108	118	57	35	12.0
29 RA	149	115	36	18	4	21	120	60	14	65	240	120	27	125	50	48	16.0
30 RA	128	103	44	22	7	26	119	60	25	74	216	109	46	137	45	46	11.0
Mean	120	112	44	22	12	25	138	69	37	77	237	119	59	122	41	37	
% of Control		93			55	114			54	112			50	103		90	
P Value‡ <		.20			.001	.20			.01	.20			.001	.50		.05	
P Value# <						.001				.001				.001			
							Subgroup 2D—Occlusion Time = 3 hours										
31 RA	133	120	55	28	4	26	180	90	20	69	305	153	31	106	41	35	12.0
32 RA	128	96	44	22	0	26	119	60	0	71	216	109	0	118	45	40	11.0
33 RA	87	82	44	22	7	17	125	63	24	51	171	86	33	71	27	28	9.5
34 RA	108	107	28	14	0	20	75	38	0	71	109	55	0	109	31	35	12.0
35 RA	109	93	35	18	2	14	101	51	6	36	160	81	9	55	37	35	10.0
36 RA	108	119	61	31	0	27	209	105	0	141	332	167	0	217	37	35	12.0
37 RA	117	99	61	31	0	33	168	84	9	105	263	131	15	178	36	41	16.0
Mean	113	102	47	24	2	23	140	70	8	78	222	112	13	122	36	36	
% of Control		90			8	96			11	111			12	109		100	
P Value‡ <		.10			.001	.50			.001	.50			.001	.50		.50	
P Value# <						.001				.01				.01			

Key to abbreviations:

C = Control observations (average of 3–10 minute periods).
½C = One-half of the control observations (approximate value for this function in each kidney).
D_1 = Observations made 3 to 5 days after occlusion of 1 renal artery for one to 3 hours.
CL = Occluded kidney. UC = Unoccluded kidney.

$$‡ = t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}.$$

= Contrasting the response of the occluded kidney as compared to the unoccluded one.

TABLE 2B. *Effect of Renal Arterial Occlusion Only on Excretion of Water and Electrolytes*

Dog Number	Urine Volume ml./min. C	½C	D1 CL	D1 UC	Plasma Sodium mEq/L C	D1	Plasma Potassium mEq/L C	D1	Urine Sodium Excretion µEq/min. C	½C	D1 CL	D1 UC	Urine Potassium Excretion µEq/min. C	½C	D1 CL	D1 UC
Subgroup 2A—Occlusion for 1 hour																
1 RA	1.1	0.6	0.3	0.6	148	141	4.15	3.94	49	25	43	103	26	13	26	15
2 RA	1.7	0.9	0.4	0.6	144	141	2.00	3.51	102	51	34	43	30	15	7	20
3 RA	0.6	0.3	1.2	0.8	130	141	3.92	4.12	123	62	156	126	28	14	23	51
4 RA	1.9	1.0	0.4	0.7	139	139	4.30	4.56	142	71	57	128	38	19	42	79
5 RA	1.3	0.7	0.9	0.7	138	135	3.76	3.10	30	15	150	127	30	15	17	16
6 RA	2.4	1.2	0.4	0.4	134	136	3.87	3.30	178	89	23	21	50	25	13	13
7 RA	1.8	0.9	1.2	2.2	131	144	3.97	3.25	119	59	95	46	53	26	33	43
8 RA	0.8	0.4	0.6	0.5	130	139	2.53	4.10	37	18	15	17	68	34	65	97
9 RA	0.8	0.4	0.2	0.3	144	144	3.76	2.84	112	56	3	8	31	16	12	22
10 RA	0.4	0.2	0.5	0.4	141	146	3.28	2.71	17	9	59	23	19	9	12	7
Mean	1.3	0.7	0.6	0.7	138	141	3.55	3.54	91	46	64	64	37	19	25	36
% of Control			86	100		102		100			139	139			132	190
P Value‡ <			.50	.50		.20		.50			.40	.40			.20	.10
P Value# <				.50		—		—				.50				.001
Subgroup 2B—Occlusion for 1½ hours																
11 RA	1.5	0.8	0.4	1.9	137	139	3.87	3.33	137	69	37	133	54	27	6	37
12 RA	1.5	0.8	0.9	0.6	141	147	3.51	3.40	37	19	80	62	35	18	31	30
13 RA	0.4	0.2	0.2	0.2	148	150	2.71	3.02	42	21	16	9	38	19	23	10
14 RA	0.2	0.1	0.2	0.2	137	154	3.17	3.33	12	6	15	14	28	14	11	10
15 RA	0.9	0.5	0.4	0.3	—	—	3.56	3.53	141	70	33	15	32	16	14	8
16 RA	0.7	0.4	1.9	0.5	134	152	2.87	2.87	41	21	169	43	48	24	25	13
17 RA	1.4	0.7	1.9	1.4	135	140	2.69	3.46	46	23	170	112	42	21	24	22
Mean	0.9	0.5	0.8	0.7	139	147	3.20	3.28	65	33	74	55	40	20	19	19
% of Control			160	140		106		103			224	167			95	95
P Value‡ <			.40	.40		.01		.50			.30	.30			.50	.50
P Value# <				.50		—		—				.50				.50

Key to abbreviations: See Table 2A.

‡ = $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$; statistical comparison of control observations with occluded and unoccluded kidney.

= Contrasting the response of the occluded kidney as compared to the unoccluded one.

TABLE 2B—*Continued*

Dog Number	Urine Volume ml./min. C	Urine Volume ml./min. ½C	Urine Volume D₁ CL	Urine Volume D₁ UC	Plasma Sodium mEq/L C	Plasma Sodium mEq/L D₁	Plasma Potassium mEq/L C	Plasma Potassium mEq/L D₁	Urine Sodium Excretion μEq/min. C	Urine Sodium Excretion μEq/min. ½C	Urine Sodium Excretion D₁ CL	Urine Sodium Excretion D₁ UC	Urine Potassium Excretion μEq/min. C	Urine Potassium Excretion μEq/min. ½C	Urine Potassium Excretion D₁ CL	Urine Potassium Excretion D₁ UC
Subgroup 2C—Occlusion for 2 hours																
18 RA	0.5	0.3	0.3	0.7	134	130	3.15	3.40	11	6	6	8	2	1	3	5
19 RA	0.7	0.4	0.0	0.4	137	130	2.74	3.53	18	9	0	2	13	7	0	7
20 RA	1.6	0.8	0.5	0.5	141	151	3.30	3.94	144	72	47	55	53	26	32	40
21 RA	1.4	0.7	0.2	0.3	145	150	3.51	4.69	121	61	36	60	45	23	29	35
22 RA	0.8	0.4	0.5	0.9	152	157	3.74	3.51	68	34	40	64	20	10	13	17
23 RA	2.1	1.0	0.6	1.3	157	152	3.43	3.76	305	152	71	192	93	47	27	35
24 RA	0.4	0.2	0.4	0.3	—	—	3.25	3.56	27	14	21	13	23	12	10	19
25 RA	0.5	0.3	0.5	0.4	145	130	3.02	3.12	22	11	8	21	12	6	9	16
26 RA	1.1	0.6	0.3	0.2	132	132	3.45	3.89	133	67	43	77	47	24	22	29
27 RA	0.6	0.3	1.1	0.4	133	128	3.05	3.23	42	21	10	52	12	6	3	7
28 RA	0.4	0.2	1.6	1.3	126	127	3.25	2.71	29	15	17	20	5	3	9	10
29 RA	0.6	0.3	0.7	0.5	132	132	3.30	3.84	33	17	3	26	7	4	10	8
30 RA	1.0	0.5	0.6	1.5	135	134	2.30	3.46	256	128	20	28	41	21	8	12
Mean	0.9	0.5	0.6	0.7	139	138	3.19	3.59	93	47	25	48	29	15	13	18
% of Control			120	140		99		113			53	102			87	120
P Value‡ <			.50	.20		.50		.05			.05	.50			.50	.10
P Value# <				.50		—		—				.05				.001
Subgroup 2D—Occlusion for 3 hours																
31 RA	1.6	0.8	0.2	0.6	134	135	2.40	3.30	65	33	5	5	17	9	1	6
32 RA	1.0	0.5	0.0	1.2	135	130	2.30	4.00	181	91	0	5	39	20	0	7
33 RA	2.0	1.0	0.8	1.0	143	131	2.80	4.00	53	27	28	41	22	11	9	11
34 RA	0.5	0.3	0.0	1.3	141	131	2.60	3.90	306	153	0	16	40	20	0	11
35 RA	0.9	0.5	0.4	1.3	137	134	2.70	3.60	45	23	3	4	26	13	3	9
36 RA	0.9	0.5	0.0	1.5	134	121	3.10	4.00	60	30	0	2	42	21	0	9
37 RA	1.2	0.6	0.3	0.5	136	131	2.90	4.00	141	71	10	28	36	18	5	14
Mean	1.2	0.6	0.2	1.1	137	130	2.69	3.83	122	61	7	14	32	16	3	10
% of Control			33	183		95		142			11	23			19	63
P Value‡ <			.01	.05		.05		.001			.05	.05			.01	.05
P Value# <				.01		—		—				.05				.001

TABLE 3A. *Effect of Aortic Occlusion Combined with Renal Arterial Occlusion*

Dog Number	Mean Blood Pressure mm. Hg		Glomerular Filtration Rate ml./min.				Renal Plasma Flow ml./min.				Renal Blood Flow ml./min.				Hematocrit		Femoral MBP During Clamp mm. Hg	Wt. in Kilo-grams
					D_1				D_1				D_1					
	C	D_1	C	½C	CL	UC	C	½C	CL	UC	C	½C	CL	UC	C	D_1		
Subgroup 3A—Occlusion Time = 2 hours																		
1 ORA	106	109	38	19	0.2	22	103	52	1	81	169	84	2	119	39	32	20	10.0
2 ORA	100	94	72	36	3.1	28	290	145	8	84	403	202	11	112	28	25	30	16.0
3 ORA	123	121	38	19	0.0	16	147	73	0	48	184	92	0	58	20	17	24	11.0
4 ORA	112	125	47	24	0.0	21	186	93	0	83	295	148	0	119	37	30	25	10.5
5 ORA	113	124	64	32	0.0	26	243	122	0	113	368	185	0	157	34	28	28	10.5
6 ORA	92	111	43	22	12.0	31	151	76	38	93	256	128	58	141	41	34	22	13.0
7 ORA	133	118	68	34	0.5	37	221	110	3	121	368	184	4	166	40	27	27	14.0
8 ORA	154	148	34	17	2.0	18	84	42	5	54	129	65	8	86	35	37	28	20.0
Mean	117	119	51	25	2.2	25	178	89	7	85	272	136	10	120	34	29	26	
% of Control		102			9	100			8	96			7	88		85		
P Value‡ <		.50			.001	.50			.001	.50			.001	.20		.05		
P Value# <						.001				.001				.001				
Subgroup 3B—Occlusion Time = 2½ hours																		
9 ORA	107	92	43	22	9.0	25	127	64	29	67	215	107	47	108	41	38	12	11.0
10 ORA	112	88	46	23	0.1	23	155	77	1	70	235	118	1	104	34	33	18	14.0
11 ORA	109	113	38	19	5.0	20	101	51	17	74	171	85	28	121	41	39	22	10.5
12 ORA	150	96	59	30	0.0	27	181	90	0	97	287	144	0	141	37	31	24	13.5
13 ORA	116	115	58	29	0.0	57	180	90	0	202	310	155	0	306	42	34	—	18.0
14 ORA	145	100	45	22	1.0	28	128	64	3	91	210	105	5	149	39	39	—	14.4
Mean	123	101	48	24	2.5	30	145	73	8	100	238	119	14	155	39	36	19	
% of Control		82			10	125			11	137			12	130		92		
P Value‡ <		.20			.001	.30			.01	.20			.01	.30		.10		
P Value# <						.01				.01				.10				

TABLE 3A—*Continued*

Dog Number	Mean Blood Pressure mm. Hg C	Mean Blood Pressure mm. Hg D_1	Glomerular Filtration Rate ml./min. C	½C	D_1 CL	D_1 UC	Renal Plasma Flow ml./min. C	½C	D_1 CL	D_1 UC	Renal Blood Flow ml./min. C	½C	D_1 CL	D_1 UC	Hematocrit C	Hematocrit D_1	Femoral MBP During Clamp mm. Hg	Wt. in Kilo-grams
Subgroup 3C—Occlusion Time = 3 hours																		
15 ORA	125	110	27	14	0.0	1	96	48	0	1	143	72	0	1	33	30	28	8.0
16 ORA	140	97	77	38	0.0	4	292	146	0	187	471	235	0	253	38	26	26	18.0
17 ORA	129	94	28	14	3.0	13	74	37	9	51	112	56	14	80	34	36	18	11.5
18 ORA	129	115	42	21	2.0	40	132	66	7	124	178	89	10	177	26	30	—	14.0
19 ORA	126	114	33	17	0.0	22	91	46	0	81	149	75	0	142	39	43	—	11.0
20 ORA	151	103	47	24	2.0	18	138	69	19	96	271	135	29	148	49	35	30	10.0
21 ORA	89	111	49	25	0.0	25	158	79	0	88	298	149	0	163	47	46	29	11.6
22 ORA	139	129	57	29	0.0	20	166	83	0	102	277	138	0	162	40	37	—	11.6
23 ORA	83	96	44	22	0.0	24	165	83	0	80	254	128	0	143	35	44	30	11.0
24 ORA	102	110	45	23	0.0	28	144	72	0	78	244	122	0	120	41	35	16	11.0
Mean	121	108	45	23	1	20	146	73	4	89	240	120	5	139	38	36	25	
% of Control		89			4	87			5	122			4	116		95		
P Value‡ <		.20			.001	.50			.001	.20			.001	.20		.50		
P Value# <						.001				.001				.001				

Key to abbreviations:

C = Control observations (average of 3–10 minute periods).
½C = One half of control observation for both kidneys—approximate renal function in each kidney (average of 3–10 minute periods).
D_1 = Observations on individual kidneys made 3 to 6 days after occlusion.
CL = Kidney on which renal artery was occluded.
UC = Kidney on which renal artery was not occluded.

‡ = $t = \bar{x}\sqrt{\frac{n(n-1)}{Sx^2}}$ ½C, used as control value for reference point.

= Contrasting the response of the occluded kidney as compared to the unoccluded one.

TABLE 3B. *Effect of Aortic Occlusion Combined with Renal Arterial Occlusion on Excretion of Water and Electrolytes*

Dog Number	Urine Volume ml./min. C	½C	D_1 CL	D_1 UC	Plasma Sodium mEq/L C	D_1	Plasma Potassium mEq/L C	D_1	Urine Sodium Excretion µEq/min. C	½C	D_1 CL	D_1 UC	Urine Potassium Excretion µEq/min. C	½C	D_1 CL	D_1 UC
Subgroup 3A—Occlusion Time = 2 hours																
1 ORA	0.4	0.2	0.1	1.3	140	134	3.51	4.43	32	16	0	4	39	20	1	12
2 ORA	3.5	1.8	0.4	1.3	144	134	3.89	3.94	617	308	17	34	44	22	7	36
3 ORA	1.2	0.6	0.0	1.9	131	152	2.89	4.56	75	38	0	23	17	8	0	17
4 ORA	0.4	0.2	0.1	1.4	146	139	3.81	3.74	31	15	0	11	28	14	1	16
5 ORA	1.1	0.5	0.0	0.8	145	150	3.07	3.64	148	74	0	7	36	18	0	16
6 ORA	1.5	0.8	0.6	0.7	153	161	3.10	3.07	99	49	75	94	38	19	18	28
7 ORA	3.1	1.5	0.1	1.0	154	157	3.35	3.48	346	173	5	96	62	31	2	43
8 ORA	0.4	0.2	0.3	1.1	135	128	3.66	3.10	31	16	13	14	15	8	3	8
Mean	1.5	0.7	0.2	1.2	144	144	3.41	3.75	172	86	14	35	35	18	4	22
% of Control			29	171		100		110			16	41			22	122
P Value‡ <			.05	.20		.50		.20			.10	.20			.01	.20
P Value# <				.001								.30				.01
Subgroup 3B—Occlusion Time = 2½ hours																
9 ORA	0.4	0.2	0.1	0.2	136	144	4.41	3.46	45	22	6	8	22	11	9	21
10 ORA	0.8	0.4	0.1	1.3	146	136	3.81	3.58	37	19	5	21	17	9	2	24
11 ORA	0.5	0.3	0.8	0.3	134	151	4.46	3.58	26	13	66	7	26	13	10	4
12 ORA	0.5	0.2	0.0	0.8	137	134	4.30	2.64	18	9	3	36	73	36	0	41
13 ORA	0.4	0.2	0.0	0.5	138	128	3.58	3.40	64	32	3	14	15	7	0	22
14 ORA	0.4	0.2	0.2	1.1	139	136	3.94	3.66	43	22	17	19	9	5	2	27
Mean	0.5	0.3	0.2	0.7	138	138	4.08	3.39	39	20	17	18	27	14	4	23
% of Control			67	233		100		83			85	90			29	164
P Value‡ <			.50	.10		.50		.10			.50	.50			.20	.10
P Value# <				.10								.50				.01

Key to abbreviations: See Table 3A.

TABLE 3B—*Continued*

Dog Number	Urine Volume ml./min. C	½C	D₁ CL	D₁ UC	Plasma Sodium mEq/L C	D₁	Plasma Potassium mEq/L C	D₁	Urine Sodium Excretion µEq/min. C	½C	D₁ CL	D₁ UC	Urine Potassium Excretion µEq/min. C	½C	D₁ CL	D₁ UC
Subgroup 3C—Occlusion Time = 3 hours																
15 ORA	1.1	0.6	0.0	0.1	136	136	3.69	5.94	108	54	0	1	17	9	0	1
16 ORA	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
17 ORA	0.4	0.2	0.3	0.5	136	140	3.84	2.84	8	4	20	19	8	4	6	10
18 ORA	1.3	0.7	0.4	0.7	130	159	3.84	3.25	13	7	35	25	12	6	7	28
19 ORA	2.8	1.4	0.0	0.7	130	130	4.72	2.92	113	57	0	75	22	11	0	18
20 ORA	0.5	0.3	0.2	1.3	130	124	3.84	2.51	99	50	3	30	41	22	0	24
21 ORA	0.5	0.3	0.1	0.9	140	128	3.12	3.51	29	15	0	12	25	13	0	8
22 ORA	1.4	0.7	0.0	1.4	128	124	4.90	2.66	62	31	0	28	19	10	0	10
23 ORA	0.6	0.3	0.0	1.0	128	126	4.22	3.64	16	8	0	28	16	8	0	18
24 ORA	5.4	2.7	0.0	1.8	143	129	3.20	2.98	156	78	0	71	33	17	0	4
Mean	1.6	0.8	0.1	0.9	133	133	3.93	3.36	67	34	6	32	21	11	1	13
% of Control			13	113		100		85			18	94			9	118
P Value‡ <			.05	.50		.50		.20			.20	.50			.01	.50
P Value# <				.01								.10				.01

the occlusion. The increase in renal function in the unoccluded kidney is probably a compensatory response. Increased function in the control kidney (unoccluded kidney) did not occur when the opposite kidney was occluded for two or three hours, perhaps due to the liberation of a renal vasoconstrictor substance by the severely damaged kidney.[2]

There was no marked or consistent difference in excretion of water and electrolytes between the two sides (Table 2B) after occlusion of a renal artery for 60 to 90 minutes, although there was a slight increase in excretion of sodium by both kidneys over control levels which was not statistically significant. In Sub-groups 2C and 2D (one kidney occluded for two and three hours), there was a statistically significant difference ($p < 0.05$) in excretion of sodium between the two sides in those animals in which one renal artery was occluded for periods of two or three hours. Excretion of potassium was also depressed in the occluded as well as in the unoccluded kidney after three hours of occlusion. There was a statistically significant ($p < 0.001$) difference between the occluded and the unoccluded kidneys after both two and three hours of occlusion, being more depressed on the occluded side. In Sub-group 2B (90 minute occlusion) and Sub-group 2D (3 hour occlusion) there was an increase and a decrease respectively in concentration of sodium in the plasma. These latter alterations were not marked and probably of little significance.

Simultaneous occlusion of the aorta and left renal artery resulted in severe functional damage to the kidney in which the renal artery was occluded for periods of two to three hours (Table 3A). The opposite kidney, although subjected to pressures below the threshold of filtration by the aortic occlusion, showed no change from control to the post occlusion observations.

Changes in urinary volume followed closely those in renal function (Table 3B). The occluded kidney showed a marked reduction in urinary volume as compared to the control observations, whereas the opposite kidney showed no change. Oftentimes the occluded kidney was completely anuric. These findings were consistent and were significant throughout whether occlusion was for two or three hours.

Levels of sodium and potassium in the plasma did not change consistently from the control to the post occlusion period although individual dogs did show variation in levels of plasma sodium. Excretion of sodium was markedly depressed from control levels in the occluded kidney. Although this reduction in excretion of sodium was usually very marked in the damaged kidney, the alterations were so variable that the significance could not be demonstrated by statistical methods. In the animals in this group there was a slight increase in excretion of potassium in the unoccluded kidney, in contrast to marked reduction in the occluded kidney.

The average mean blood pressure in the distal segment during the period of occlusion was 26 mm. Hg and 19 mm. Hg and 25 mm. Hg, respectively, for Groups 3A, 3B and 3C.

DISCUSSION

Apparently in the dog, renal ischemia as produced by occlusion of a renal artery for periods up to two hours will not always produce significant functional renal damage; but for the group as a whole there is a slight but significant depression in renal function even after one hour of occlusion. After two hours of occlusion renal function is usually but not always depressed and after three hours of occlusion, it is always severely depressed on the occluded side ($p < 0.001$). The contralateral kidney is not affected and function may actually increase in this kidney, apparently a compensatory response. These deductions are in keeping with observations made previously by Van Slyke [11] and others.[10] Like-

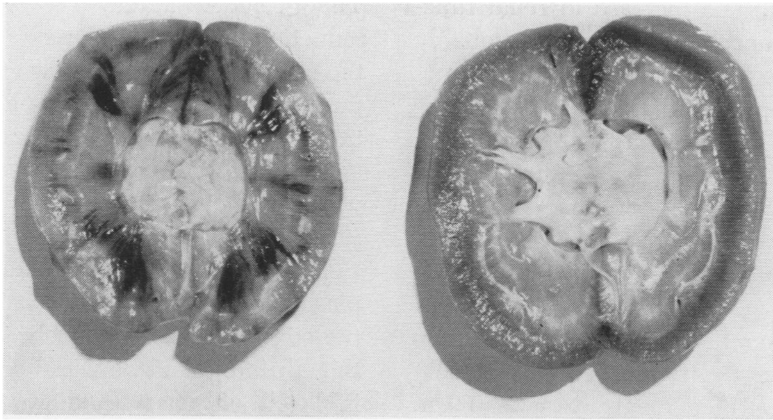

FIG. 2. Gross changes in the kidney showing the difference between the effect of renal arterial occlusion (left) alone for two hours as contrasted to the unoccluded kidney in which there were no gross pathologic alterations.

FIG. 3. Gross changes in the kidney exposed to aortic occlusion (right) as compared to the effect of aortic plus renal arterial occlusion (left) for two hours. There was no gross evidence of damage to the right kidney which was exposed to aortic occlusion alone. However, the left kidney was severely damaged and showed considerably more gross changes than those seen on the left kidney in Figure 2 which was exposed to renal arterial occlusion, without concurrent aortic occlusion, for a similar period of time.

wise, it is apparent that occlusion of the aorta proximal to the renal arteries for periods up to three hours with resulting mean blood pressures below 30 mm. Hg in the distal segment produces no functional renal damage (Groups 1 and 3). The most severe damage to the kidney results when both the renal artery and the aorta proximal to the renal arteries are occluded. In the current studies occlusion of a renal artery alone for three hours produced about the same degree of damage as simultaneous renal artery and aortic occlusion for only two hours. Figure 2 demonstrates the gross changes observed by two hours of occlusion of the renal artery (left) only; whereas Figure 3 demonstrates the effect of simultaneous renal artery and aortic occlusion for two hours. The differences in the degree of renal changes are striking. There was no apparent damage to the right kidney in Figure 3 which was exposed to aortic occlusion only for two hours.

These observations suggest that mean blood pressure below 30 mm. Hg, which is less than that required for the production of irreversible shock, will not produce functional renal damage for periods up to three hours. Although renal clearance at the time of reduced blood pressure (sub-filtration pressure) is zero there is enough blood circulating through the kidney at these reduced pressures to prevent significant renal damage. Apparently as long as a minimal amount of blood circulates through the kidney, it suffices to keep the renal parenchyma viable.

The circulation through the renal capsule to the cortex may be of greater importance than is usually considered to be the case and may indeed play an important role in the renal circulation. The last consideration is based upon the fact that renal arterial occlusion alone for two hours does not produce as severe functional damage as when renal arterial occlusion is combined with aortic occlusion (hypotension of the distal segment), then severe renal damage is produced in every case. This suggests that when the renal artery alone is occluded, the systemic blood pressure in the tissues surrounding the kidney remains unaltered, and consequently remains sufficiently high to maintain some blood flow through the renal capsule. This is frequently enough to keep the kidney viable for as long as two hours. Conversely, if one occludes one renal artery and the aorta simultaneously, resulting in hypotension in the distal segment, then the blood pressure in the surrounding tissues is reduced to the point at which very little or no blood flows through the renal capsule to the cortex which results in complete renal ischemia and necrosis.

Whether or not complete renal ischemia results during shock remains to be proven. Experiments are now in progress to obtain additional information concerning this point. If it can be shown that any circulation through the kidney exists during shock, then renal failure should rarely result from ischemia due to hypotension alone and the cause must lie elsewhere since the animal (or man) would die of cerebral ischemia before he developed renal ischemia of sufficient duration to produce severe renal damage. In conclusion, it appears that reduction in blood pressure alone (equivalent to those found in irreversible shock), will not of itself produce acute renal failure (lower nephron nephrosis).

SUMMARY AND CONCLUSIONS

1. The effect of renal ischemia produced by three different methods of arterial occlusion has been observed in 79 dogs using clearance studies as an indication of the degree of renal functional impairment. Renal ischemia was produced for periods up to three hours by occlusion of the aorta above the renal arteries, by occlusion of one renal artery alone, and, in the third group, by occlusion of the renal artery and the aorta simultaneously. Three to five days after the ischemia was produced by the various methods, follow up studies of renal function were carried out and these were compared to similar observations made prior to the production of ischemia.

2. Occlusion of the aorta above the renal arteries resulted in a maintained arterial blood pressure distal to the occlusion of 30 mm. Hg or less. This pressure was apparently enough to maintain adequate circulation through the kidneys to prevent renal damage for periods of occlusion up to three hours.

3. Occlusion of one renal artery alone produced renal damage in some dogs even after one hour. The response to renal arterial occlusion alone was very variable since some animals withstood occlusion for periods up to two hours without significant renal damage. However, after three hours of occlusion, severe renal damage resulted in all of the animals studied.

4. The most severe damage resulted from combined aortic and renal arterial occlusion. Even after two hours of occlusion, renal damage was marked in all animals and after three hours, renal function was completely destroyed. The degree of renal damage in this group of animals after two

hours of occlusion was approximately equivalent to that in animals in which one renal artery alone was occluded (without concurrent aortic occlusion) for three hours. This suggests that, under the conditions of the experiment, there was frequently an adequate amount of blood reaching the parenchyma of the kidney via the cortex to prevent severe and consistent renal damage for a period of two hours during which time the renal artery was occluded. This further suggests that there is more potential collateral circulation through the renal cortex than is usually considered to be the case.

5. When operative procedures are employed in which the circulation to the kidney is to be interrupted, it might be very helpful if only a small amount of blood could be by-passed from the systemic circulation into the renal parenchyma. Thus irreversible renal damage could be prevented for long periods of time.

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